REMARKS

Reconsideration of this application is respectfully requested in view of the following remarks.

I. Status of the Claims. Upon entry of this amendment, claims 1, 2, 4-19, and 21-25 are pending.

Claim 1 has been amended without prejudice or disclaimer, to provide that the claimed method excludes the use of metoclopramide. Support for the amended claim is found in the specification at, *e.g.*, p. 6, paragraph [0099] ("'prolactin enhancer' includes prolactin ... antiemetics, e.g., metoclopramide ...."). As a threshold matter, it is noted that amending claim 1 to exclude metoclopramide from the prolactin enhancers called for in the claims does not constitute new matter. [MPEP 2173.05(i) *citing In re Johnson,* 558 F2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977). (Applicants may exclude embodiments enumerated in the specification. "[The] specification, having described the whole, necessarily described the part remaining.")].

Claim 3 has been cancelled without prejudice or disclaimer.

Claim 25 has been added. Claim 25 calls for the administration of prolactin in the claimed method. Support is found in the specification at, *e.g.*, p. 6, paragraph [0099]; Example 1, which appears at p. 10, paragraph [0140]; Example 2, which appears at pp. 10-11, paragraphs [0141] – [0143]; and Example 3, which appears at p. 11, paragraphs [0144] – [0146]. Thus, the new claim does not add new matter.

All claim amendments are made without prejudice or disclaimer. Applicants specifically reserve the right to file one or more continuation application to pursue any subject removed from the claims by amendment.

By this Amendment, no new matter has been added to the application.

II. Claim Rejections. The claim rejections set forth in the Final Office Action are summarized and addressed as follows.

(i) Rejections for Obviousness-Type Double Patenting and Under 35 U.S.C. §103 over U.S. Patent No. 5,792,748, Werning, and Cincotta

Claims 1-3, 6, 10, 15, 21 and 22 stand rejected under the judicially created doctrine of obviousness-type double patenting, as allegedly obvious over claims 3, 8, 13 and 19 of U.S. patent no. 5,792,748 (the '748 patent) in view of Werning et al., *Arch. Ontolaryngol. Head Neck Surg.* 121:783-789 (995) ("Werning") and Cincotta et al., *Cancer Res.* 54:1249-1258 (1994) ("Cincotta"), as evidenced by Molitch, *Endocrinol. Metab. Clin. North Am.* 21:(4) (abstract) (1992) ("Molitch").

Claims 1-19, and 21-24 stand rejected as allegedly obvious over the '748 patent in view of Werning and Cincotta as evidenced by Molitch.

In response, without conceding the soundness of the rejection, claim 1 has been amended to exclude metoclopramide from the prolactin enhancers called for in the claims, and claim 3 has been cancelled.

The claims are drawn to treating tumors in a mammal with PDT in combination with NRT using a prolactin enhancer, i.e., administering the prolactin enhancer at appropriate time intervals of day such that the daily plasma prolactin profile of a tumor bearing mammal conforms to or approaches the normal daily plasma prolactin profile for healthy members of the same species and sex of the mammal. The prior art cited by the Examiner discloses treating tumors separately with PDT or NRT, but not in combination. The Examiner's position is that the cited references teach that the combination of photodynamic therapy with administration of a prolactin enhancer results in the increased regression of tumors versus photodynamic therapy alone. Specifically, the Examiner contends that the '748 patent discloses and claims a method for inhibiting neoplasm growth in humans by comparing the prolactin profile of the afflicted human to a standard prolactin profile for healthy humans of the same sex and adjusting the prolactin profile of the afflicted human via administration of a prolactin enhancer, such as melatonin in a certain amount and at certain times. The Examiner also asserts that Werning discloses that the combination of photodynamic therapy with metoclopramide increases the percentage of tumor regression versus photodynamic therapy alone. The Examiner cites Molitch for evidence that metoclopramide is a prolactin

enhancer. According to the Examiner, it would have been obvious to one of ordinary skill in the art to optimize the invention claimed in the '748 patent so as to include PDT.

The subsisting claims are not obvious over the prior art cited by the Examiner at least because Werning's teachings are restricted solely to metoclopramide. Werning is directed solely to the use of metoclopramide to enhance the effect of photodynamic therapy. This is evidenced throughout Werning, indeed starting with its title, which recites that metoclopramide "enhances the effect of photodynamic therapy ...." Werning states explicitly that "our research efforts are aimed toward improving the clinical response to PDT" (Werning, p. 788, top of column 2), that the experimental goal was to "assess the potentiating effects of metoclopramide" (Werning, p. 785, column 1, first full paragraph), and metoclopramide is "used to enhance the effects of ionizing radiation and chemotherapy" (*see, e.g.*, p.785, column 1, second full paragraph). Nowhere does Werning, however, fails to teach the use of any substance other than metoclopramide to enhance the effects of PDT and fails to suggest that any substance that could or should be employed in prolactin resetting therapy.

Each of the obviousness rejections relies on Werning to provide a link between PDT and NRT that is otherwise absent from the cited references. Because the subsisting claims exclude metoclopramide, however, Werning fails to provide any link between the combination of PDT and NRT recited in the clainms. Because each of the instant obviousness rejections relies on Werning, they all should be withdrawn.

(ii) Rejection for Obviousness-Type Double Patenting over the '914 Patent in view of Lin and Cincotta

Claims 1-4, 10, 15, and 21 stand rejected for obviousness-type double patenting over claims 12, 13, 28 and 30 of Cincotta et al., U.S. Patent No. 6,071,914 ("the '914 patent"), in view of Lin, *Cancer Cells*, 1991, 3:4.

In partial response, claim 3 has been cancelled.

Applicants traverse. The claims are not obvious over the combination of the teachings of the cited references because unexpected results are obtained with the combination of neuroendocrine resetting therapy and PDT, compared to either therapy alone. Examples 1 and 2 and Figure 5 of the application demonstrate the synergistic effects when PDT is combined with NRT using a prolactin enhancer, as called for in the claims. There is no suggestion in the prior art that such synergistic effects could be achieved.

Thus, Example 1, set forth on page 28 of the instant specification, describes an experiment designed to measure the effect of control (C), prolactin (PRL; 20 mcg/mouse at 10 h after light onset at 7 days after tumor inoculation, continuing for 14 days), PDT (D+L; EtNBS photosensitizer; power density of 100J/cm^2 and a total energy of 100J/ cm^2) and prolactin plus PDT (D+L+PRL) treatments on tumors in EMT-6 tumor bearing mice. The results of the experiment that are shown in Figure 5 demonstrate the unexpected synergistic effect of the combined treatment.

As shown in Figure 5, the average tumor volume in EMT-6 tumor bearing animals treated with prolactin alone was found to be 56% of the average tumor volume in control animals. The average tumor volume in EMT-6 tumor bearing animals treated with PDT alone was 43% of the average tumor volume for control animals. Thus, with either treatment alone, on average approximately 50% tumor volume remained after treatment, as compared to control animals. However, when the treatments were combined, average tumor volume was dramatically reduced to **7.6%** of the average tumor volume in control animals. These results are unexpected and show that a combination of PDT and NRT produces a synergistic effect in reducing the growth rate of or eradicating tumors, as stated in the specification at p. 10, paragraph [0138].

Further experimental evidence of the synergy obtained in treating tumors with a prolactin enhancer and PDT is set forth in Example 2 (see specification at pages 28-29). Example 2 reports that, when PDT with the benzophenothiazine photosensitizer EtNBS is used alone, at a power density of 50 mW/ cm^2 and a total energy of 180 J, tumor "cure" (tumor-free for at least 90 days) of 4-8 mm diameter tumors can be achieved in 70-100% of the cases, and is largely dependent upon the tumor size at the time of PDT. In contrast, if intraperitoneal prolactin is administered (20

mcg/mouse/day at 10 h after light onset, starting from day of tumor cell inoculation) in conjunction with PDT, then the cure rate is 100%. Furthermore, the time course of tumor eradication is significantly faster with the combined treatment versus PDT alone. Hence, tumors remained noticeable 48-72 h following PDT treatment alone, taking 14 days to regress completely, with eschar formation at 24-48 hours. In contrast, when timed administration of prolactin was combined with PDT, 100% of the treated animals exhibited eschar formation and complete tumor eradication within 24 h of PDT. Hence, in Example 2, the combination of neuroendocrine resetting therapy and PDT lead to more rapid tumor eradication and a higher tumor eradication rate (i.e., 100%), compared to PDT alone. Again, this is unexpected and indicative of a synergistic effect when PDT and NRT are combined, as stated in the specification.

Moreover, the timing of prolactin administration is essential in order to obtain the synergistic effect of PDT and prolactin treatment. The specification makes it clear that prolactin should be administered during the time of the plasma prolactin peak in a healthy mammal of the same sex.

IV. New Claim 25.

New claim 25 recites the use of prolactin in the claimed method. Claim 25 is patentable over the prior art for at least the reasons set forth above in connection with the currently pending claims. Claim 25 further complies with all requirements set forth in 35 U.S.C. §§ 101 and 112. Allowance of claims 1, 2, 4-19, and 21-25 is requested.

IV. Conclusion.

In view of the above amendment and arguments presented, applicant believes the pending application is in condition for allowance.

Dated: October 27, 2008

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